II. REMARKS

Preliminary Remarks

Amendment of the specification

The first paragraph of the specification is amended to show the current status of U.S. Patent Application No. 09/853,581.

The paragraph beginning on line 8 of page 12 is amended by adding the word "is" in correction of an obvious error.

The paragraph beginning on line 1 of page 18 describing the experimental data shown in Figure 2A is amended to identify the antigen of the disclosed example as E7 rather than ovalbumin, in correction of an obvious error.

Amendment of the claims

Claim 47 is amended to refer to the adjuvant formulation as an "antigen-containing adjuvant formulation" for greater clarity, and to identify the cancer cells as cervical cancer cells as described, for example on page 15, line 15. Step (b) of claim 47 is further amended to identify the agent that is capable of neutralizing, blocking, antagonizing, or down regulating the activity or preventing activation of TGFβ as one that is selected from the group consisting of an anti-TGFβ antibody, a TGFβ receptor-fusion protein, a TGFβ receptor Fc-fusion protein, an anti-TGFβ receptor antibody that blocks the interaction of TGFβ and TGFβ receptor, and a thrombospondin peptide that binds to TGFβ and inhibits TGFβ activity, as described in the specification, for example, from line 8 of page 9 to line 2 of page 10.

The amendment incorporates into claim 47 subject matter of claims 48-50, 66, and 67, which are canceled.

Claims 47, 51-65 and 68 are pending.

Patentability Remarks

Objection to abbreviations in the claims

The examiner objects to claims 48, 49, and 66, because of references in the claims to the abbreviations "TGF" and "TGFβR." As pointed out above, claims 48, 49 and 66 to which the objection is directed are canceled. The applicants submit that the meaning of previous claims 48, 49, and 66 is clear in view of the specification, in compliance with 37 C.F.R. §1.75(d)(1). However, in order to expedite prosecution, claim 47 is amended by inserting the abbreviation "TGFβ" within parentheses following the term "transforming growth factor-β," and the term "TGFβR" that is incorporated into claim 47 from claims 48, 49, and 66 is replaced with the term "TGFβ receptor." Withdrawal of the objection is respectfully requested.

35 U.S.C. §112, First Paragraph, Written Description - New Matter

Claim 64 is rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly does not describe the claimed method "wherein the antigen formulation contains no more than 20 micrograms of an immunostimulating muramyl dipeptide" in such a way as to convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed, in compliance with the requirement for written description of 35 U.S.C. §112, first paragraph. The examiner alleges that the specification "only teaches not to use muramyl dipeptide" and that "there is nothing in the specification to teach or suggest to **use** an antigen formulation containing no more than 20 micrograms of an immunostimulating muramyl dipeptide in the claimed method...." *See* page 12 of the official action. In support of this allegation, the examiner points to two sentences on lines 9-11 of page 12, which teach that it is important that a muramyl dipeptide (MDP) be lacking from the adjuvant formulation of the invention, because "such a peptide will interfere with induction of a CTL response if it [is] provided in an amount greater than about 20 micrograms per normal human formulation administration."

The applicants submit that the specification **does** describe the method of claim 64 in a manner such that one of skill in the art at the time the application was filed would recognize that that the inventors had possession of the claimed invention "wherein the antigen formulation

contains no more than 20 micrograms of an immunostimulating muramyl dipeptide." The paragraph on page 12 of the application that contains the sentences cited by the examiner goes on to describe that: "It is preferred that such peptides are completely absent from the antigen formulation, despite their apparent stimulation of the humoral compartment of the immune system. That is, although such peptides may enhance the humoral response, they are disadvantageous when a cytotoxic T-lymphocyte response is desired." (*See* page 12, lines 12-16). The paragraph beginning on line 8 of page 12 thus describes the invention wherein peptides such as MDP are completely absent as a "preferred embodiment," it describes that peptides such as MDP can provide the advantage of enhancing the humoral response, and it expressly describes that more than 20 micrograms of a peptide such as MDP interferes with induction of a CTL response. One of skill in the art would clearly understand that the description on page 12 of the importance that an MDP be "lacking" from the adjuvant formulation of the invention does not simply describe complete absence of MDP from the adjuvant formulation, but also describes the method of the invention in which MDP is present in an amount sufficiently low (*i.e.*, $\leq$ 20 micrograms per normal human formulation administration) that the MDP does not interfere with induction of a CTL response. One of skill in the art would therefore understand from the description provided by the specification that the disclosed invention includes and can be practiced as a method wherein the antigen formulation contains no more than 20 micrograms of an immunostimulating MDP. Accordingly, the reference to such a method in claim 64 is not new matter, and withdrawal of the rejection of claim 64 under 35 U.S.C. §112, first paragraph, for alleged lack of written description is respectfully requested.

35 U.S.C. §112, Second Paragraph

Claims 63-65 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite because the reference to "the antigen formulation" in claim 52 is considered to lack antecedent basis in claim 52, which refers to an "adjuvant formulation."

The applicants submit that proper antecedent basis for the reference in claims 63-65 to "the antigen formulation" is found on line 2 and on the last line of claim 52, which refer expressly to an "antigen formulation." Withdrawal of the rejection of claim 63-65 under 35 U.S.C. §112, first paragraph, is therefore respectfully requested.

35 U.S.C. §112, First Paragraph, Written Description

Claims 47, 48, 50-65 and 68 are rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly does not describe an "at least one agent that is capable of neutralizing, blocking, antagonizing, or down regulating the activity or preventing activation of transforming growth factor-β" as specified in step (b) of claim 47, a TGFβ analog or a TGFβ binding protein as specified in claim 48, or a full-length thrombospondin peptide, in such a way as to convey to one skilled in the relevant art that the inventors had possession of the claimed method at the time the application was filed, in compliance with the requirement for written description of 35 U.S.C. §112, first paragraph. As pointed out above, claims 48 and 50 of the rejected claims are canceled.

The applicants do not agree that the rejected claims lack description in the specification in compliance with the written description requirement of 35 U.S.C. §112, first paragraph. However, in order to expedite prosecution, part (b) of claim 47 is amended to identify the agent that is capable of neutralizing, blocking, antagonizing, or down regulating the activity or preventing activation of TGFβ as one that is selected from the group consisting of an anti-TGFβ antibody, a TGFβ receptor-fusion protein, a TGFβ receptor Fc-fusion protein, an anti-TGFβ receptor antibody that blocks the interaction of TGFβ and TGFβ receptor, and a thrombospondin peptide that binds to TGFβ and inhibits TGFβ activity. As noted above, explicit description of the agents capable of neutralizing, blocking, antagonizing, or down regulating the activity or preventing activation of TGFβ specified in amended claim 47 is found in the specification, for example, from line 8 of page 9 to line 2 of page 10. The agents specified in part (b) have in common the property that they are polypeptides that inhibit the biological activity of TGFβ, and so form a proper Markush group pursuant to M.P.E.P. § 2173.05(h). Withdrawal of the rejection of claims 47, 48, 50-65 and 68 under 35 U.S.C. §112, first paragraph, for alleged lack of written description is respectfully requested.

35 U.S.C. §112, First Paragraph, Scope

Claims 47-68 are rejected under 35 U.S.C. §112, first paragraph, because the specification is considered to enable a method for enhancing an antigen-specific cytotoxic T cell lymphocyte (CTL) response against cervical cancer comprising administering: (a) an adjuvant formulation comprising a human papillomavirus E7 protein, and (b) an agent selected from the group consisting of an antagonistic anti-TGFβ antibody, a TGFβ receptor-fusion protein, or a TGFβ receptor Fc-fusion protein, but allegedly does not enable one of skill in the art to use the claimed method for enhancing an antigen-specific CTL response against "cancer cells" wherein step (b) comprises administering "at least one agent that is capable of neutralizing, blocking, antagonizing, or down regulating the activity or preventing activation of" TGFβ, a TGFβ analog, a TGFβ binding protein, or a full-length thrombospondin peptide. *See* page 18 of the official action. As pointed out above, claims 48-50, 66, and 67 of the rejected claims are canceled.

The applicants submit that the specification enables one of skill in the art to successfully practice the method as previously claimed without the need for undue experimentation; however, in order to expedite prosecution, claim 47 is amended to identify the cancer cells as cervical cancer cells, and step (b) of claim 47 is amended to identify the agent that is capable of neutralizing, blocking, antagonizing, or down regulating the activity or preventing activation of TGFβ as one that is selected from the group consisting of an anti-TGFβ antibody, a TGFβ receptor-fusion protein, a TGFβ receptor Fc-fusion protein, an anti-TGFβ receptor antibody that blocks the interaction of TGFβ and TGFβ receptor, and a thrombospondin peptide that binds to TGFβ and inhibits TGFβ activity, as described in the specification, *e.g.* from line 8 of page 9 to line 2 of page 10. In addition to the agents identified by the examiner as having enabling description, *i.e.*, an anti-TGFβ antibody, a TGFβ receptor-fusion protein, and a TGFβ receptor Fc-fusion protein, the amended claim specifies an anti-TGFβ receptor antibody that blocks the interaction of TGFβ and TGFβ receptor, as described for example at page 9, lines 18-19, and a thrombospondin peptide that binds to TGFβ and inhibits TGFβ activity, as described for example at page 9, line 19 to page 10, line 2. The application describes thrombospondin peptides that bind to TGFβ and inhibit TGFβ activity by blocking the binding of TGFβ to TGFβ receptor or by preventing the activation of latent TGFβ, and teaches that such thrombospondin peptides were

known at the time the application was filed, and one of skill in the art would understand from the description provided by the specification that a thrombospondin peptide that activates TGFβ is not to be used for the claimed method. The applicants submit that the description of the invention provided by the specification enables one of skill in the art to successfully practice the method of the claims as presently amended without having to perform undue experimentation. Withdrawal of the rejection of claims 47-68 under 35 U.S.C. §112, first paragraph, for lack of enablement is therefore respectfully requested.

35 U.S.C. §103(a)

- Claims 47, 48, 50-63, and 65-68 are rejected under 35 U.S.C. §103(a) as allegedly being obvious in view of Raychaudhuri et al. (U.S. Patent No. 5,695,770) combined with Woodworth et al. (1996), and Segarini et al. (WO 94/09815), as evidenced by Schmolka et al. (1977).

Obviousness under 35 U.S.C. §103 is a legal conclusion involving a preliminary determination of four factual inquiries: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the pertinent art; and (4) secondary considerations of nonobviousness, which include objective indicia of nonobviousness such as commercial success, long-felt but unsolved need, and failure of others. Graham v. John Deere Co., 383 U.S. 1, 17-18, 148 U.S.P.Q. 459, 467 (1966).

To establish a *prima facie* case of obviousness, the examiner must show that the prior art references themselves or the knowledge generally available to one of ordinary skill in the art would (1) provide some suggestion or motivation to modify or combine reference teachings to obtain the claimed invention, (2) teach or suggest all of the claim limitations, and (3) provide a reasonable expectation that the claimed invention can be made or used successfully. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *See* In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991), *also* In re Dance, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998) citing In re Raynes, 7 F.3d 1037, 1039, 28 USPQ2d 1630, 1631 (Fed. Cir. 1993); In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992), *and* M.P.E.P. § 2142.

With respect to the scope and content of the prior art, the primary reference, Raychaudhuri et al., describes a method for treating cervical cancer comprising administering a composition comprising a papillomavirus antigen such as HPV E7 protein mixed with a microfluidized antigen formulation comprising (i) a stabilizing detergent, (ii) a micelle-forming agent, and (iii) a biodegradable and biocompatible oil, wherein the antigen formulation is formulated as a stable oil-in-water emulsion, wherein the composition is capable of inducing a CTL response against the papillomavirus antigen (*e.g.*, *see* claim 3). Raychaudhuri et al. does not describe or suggest the claimed method for enhancing an antigen-specific CTL response against cervical cancer cells in a patient comprising administering an adjuvant formulation comprising a HPV E7 protein capable of inducing a CTL response specific for said HPV E7 protein in combination with an agent that inhibits the activity of TGFβ as specified in claim 47 as amended.

Segarini et al. teaches that TGFβ can cause immunosuppression and suggests administering an anti-TGFβ antibody to counteract the immunosuppression (*see* p. 2, second paragraph), and the reference describes administering a TGFβ-binding receptor fragment to increase the effectiveness of a vaccine (*see* p. 6).

Woodworth et al. describes an in vitro cell culture system in which it is shown that TGFβ1 stimulates the growth of HPV-immortalized keratinocytes, and hypothesizes that TGFβ1 may stimulates the growth of HPV-infected cells in vivo (*see* page 817, right column).

Schmolka et al. describes the chemical structure of poloxamer 401.

The examiner alleges that at the time the invention was made it would have been obvious for one of ordinary skill in the art to modify the method of Raychaudhuri et al. by co-administering a TGFβ-antagonizing agent such as an anti-TGFβ antibody or a TGFβ-binding receptor fragment, since inhibition of TGFβ activity would allegedly have been expected to increase vaccine efficacy as described by Segarini et al., and to prevent TGFβ from stimulating growth of HPV-infected cells as described by Woodworth et al.

The applicants respectfully submit that the cited references do not establish a *prima facie* case of obviousness, because Raychaudhuri et al. does not describe or suggest the presently claimed method, and Woodworth et al. (1996) and Segarini et al. (WO 94/09815), as evidenced by Schmolka et al. (1977), would not have provided suggestion or motivation to one of ordinary

skill in the art to modify the method of Raychaudhuri et al. to obtain the claimed invention with a reasonable expectation of success.

The present application demonstrates the surprising and unpredictable discovery that in a method in which a composition comprising a papillomavirus HPV E7 protein mixed with a microfluidized antigen formulation according to the invention of Raychaudhuri et al. is administered to a subject with HPV E7 expressing tumors with negligible effect on the tumors, administration of the combination of an adjuvant formulation comprising HPV E7 protein and a TGFβ-antagonizing agent according to the presently claimed invention strongly inhibits the growth of the HPV E7 expressing tumors in the treated subject. *See* Example 2, pages 17-18, and Figure 2A.

The level of skill of one of ordinary skill in the art pertinent to the claimed invention, which relates to the development and use of methods for treating cancer, is relatively high. Practitioners typically have M.D. and/or Ph.D. degrees and years of post-doctoral training. At the time the invention was made, the effect of blocking or antagonizing TGFβ on the growth of HPV E7 expressing tumor cells in vivo was unknown and unpredictable by such persons of ordinary skill in the pertinent art. As described by Woodworth et al., at the time the invention was made, TGFβ was known to inhibit the growth of some HPV-immortalized cell lines, and to induce other HPV-immortalized cell lines to undergo apoptosis (*see* p. 817, right column). Braun et al. (Mol. Carcinog., 1992, 6(2):100-111, abstract attached) teach that TGFβ inhibits the growth of HPV-immortalized cells that are resistant to in vitro differentiation signals. Jacobberger et al. (Exp. Cell Res., 1995, 220(2):390-6, abstract attached) similarly teaches that growth of HPV-immortalized cervical cells in vitro is inhibited by TGFβ, and Rorke et al. (Exp. Cell Res., 1995, 216(1):65-2, abstract attached) describes an HPV16-immortalized cervical cell line that induced by TGFβ to undergo apoptosis. Ozbun et al. (J. Virol., 1996, 70(8):5437-46) states that there are "conflicting reports on the ability of TGFβ1 to inhibit the growth of HPV-positive keratinocytes in monolayer cultures," it describes a tissue culture system "that more accurately mimics the in vivo cellular environment and architecture," and it teaches that TGFβ1 promotes the differentiation of HPV-positive keratinocytes in said tissue culture system. As there were conflicting reports on the ability of TGFβ1 to inhibit the growth of HPV-positive cells in the published scientific literature available at the time the invention was made, as noted by

Ozbun et al. and Woodworth et al., and as the experimental results described by the above-discussed references show that TGFβ can inhibit the growth and/or induce apoptosis of HPV-infected cervical cells, one of ordinary skill in the art could not have predicted the result of combining the administration of a composition comprising HPV E7 protein that is capable of inducing a CTL response against the HPV E7 protein as described by Raychaudhuri et al. with administration of an agent such as an anti-TGFβ antibody or a TGFβ-binding receptor fragment that antagonizes TGFβ. From the teachings of the published scientific literature, one of ordinary skill in the art would have considered it possible that such a method could actually result in stimulation of the growth of HPV E7 expressing tumor cells in the treated subject. The combination of Raychaudhuri et al. with Woodworth et al. (1996) and Segarini et al. (WO 94/09815), as evidenced by Schmolka et al. (1977), therefore would not have provided suggestion or motivation to one of ordinary skill in the art to modify the method of Raychaudhuri et al. to obtain the claimed invention with a reasonable expectation of success. Accordingly, the cited references do not establish a *prima facie* case of obviousness, and the applicants respectfully request that the rejection of claims 47, 48, 50-63, and 65-68 under 35 U.S.C. §103(a), as allegedly being unpatentable in view of Raychaudhuri et al. (U.S. Patent No. 5,695,770) combined with Woodworth et al. (1996), and Segarini et al. (WO 94/09815), as evidenced by Schmolka et al. (1977), be withdrawn.

- Claim 49 is rejected under 35 U.S.C. §103(a) as allegedly being obvious in view of Raychaudhuri et al. (U.S. Patent No. 5,695,770) combined with Woodworth et al. (1996), and Segarini et al. (WO 94/09815), as evidenced by Schmolka et al. (1977), and further in view of Schultz-Cherry et al. (1995) or Capon et al. (WO 91/08298). As pointed out above, claim 49 is canceled, and this ground of rejection is addressed by the applicants as if it is directed to claim 47 to the extent that claim 47 incorporates the subject matter of canceled claim 49.

This ground of rejection is premised on the examiner's argument that at the time the invention was made it would have been obvious for one of ordinary skill in the art to modify the method of Raychaudhuri et al. comprising administering a composition comprising HPV E7 protein that is capable of inducing a CTL response against the HPV E7 protein, by co-administering a TGFβ-antagonizing agent in order to increase vaccine efficacy as described by

Segarini et al., and/or to prevent TGFβ from stimulating growth of HPV-infected cells as described by Woodworth et al., as discussed above. Schultz-Cherry et al. is further cited for its description of a thrombospondin peptide that binds to TGFβ and inhibits activation of latent TGFβ, and Capon et al. is further cited for its description of a TGFβ receptor Fc-fusion protein.

As discussed above with respect to the rejection of claims 47, 48, 50-63, and 65-68 under 35 U.S.C. §103(a) as allegedly being obvious in view of Raychaudhuri et al. combined with Woodworth et al. and Segarini et al., as evidenced by Schmolka et al., the cited references do not establish a *prima facie* case of obviousness, because Raychaudhuri et al. does not describe or suggest the presently claimed method, and the cited secondary references would not have provided suggestion or motivation to one of ordinary skill in the art to modify the method of Raychaudhuri et al. to obtain the claimed invention with a reasonable expectation of success. The failure of the cited references to establish a *prima facie* case of obviousness is not remedied by the additional teachings of Schultz-Cherry et al. and/or Capon et al. The applicants therefore respectfully request that the rejection of claim 49 under 35 U.S.C. §103(a), as allegedly being unpatentable in view of Raychaudhuri et al. (U.S. Patent No. 5,695,770) combined with Woodworth et al. (1996), and Segarini et al. (WO 94/09815), as evidenced by Schmolka et al. (1977), and further in view of Schultz-Cherry et al. (1995) or Capon et al. (WO 91/08298), also be withdrawn.

Nonstatutory obviousness-type double patenting

Claims 47-68 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 and 4-19 of U.S. Patent No. 6,998,125.

A terminal disclaimer executed by the undersigned will be considered when allowable claims have been noted.

III. IN CONCLUSION

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If the examiner identifies any points that he feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

No official fees are believed to be due, however, please charge any fees associated with the submission of this response to Deposit Account Number 03-3975.

Respectfully submitted,

/thomas a cawley jr/

Date: December 8, 2006 By_____

Thomas A. Cawley, Jr., Ph.D.
Reg. No. 40944
Tel. No. 703.770.7944
Fax No. 703.770.7901

PILLSBURY WINTHROP SHAW PITTMAN LLP
P.O. Box 10500
McLean, VA 22102
703.770.7900